Mayo Clinic Tumor Rounds

OSTEOSARCOMA IN A PATIENT WITH POLYOSTOTIC FIBROUS DYSPLASIA AND ALBRIGHT'S SYNDROME

*Pietro Ruggieri, MD, PhD**
*Franklin H. Sim, MD**
Jeffrey R. Bond, MD†
K. Krishnan Unni, MB, BS§

A 36-year-old woman was seen initially at the Mayo Clinic in August 1967 for a cystic lesion in the ribs which had been discovered incidentally on chest radiographs obtained 3 weeks before referral. The patient had several pigmented skin areas on her face and back which she said she had "always had." These pigmented areas were large and had irregular margins (Fig 1). The patient had begun to have irregular menses at about age 7 and had pubertal changes around age 9. She had a history of several pathologic fractures, all treated conservatively. She had fractured the right tibia in 1958, the right femur in 1959, and the right wrist in 1966. She had had hypertension since her youth. Radiographs taken of the whole skeleton showed a ground-glass appearance, typical of fibrous dysplasia, in the pelvis, both femurs, right tibia, right ulna and radius, and several ribs (Fig 2). No other abnormalities were evident on physical examination or laboratory tests. Serum alkaline phosphatase levels were normal. She was dismissed with a diagnosis of polyostotic fibrous dysplasia and Albright's syndrome.[1]

Four years later, in July 1971, the patient was again seen at the Mayo Clinic for pain in her left hip of 9 months' duration. Laboratory tests showed a marked increase of serum alkaline phosphatase levels.[2] Radiographs of the pelvis revealed a malignant lesion clearly extruded outside the bone, with a huge soft tissue mass expanding into both the pelvis and the gluteal region. Conspicuous osseous destruction and a slightly mineralized large soft tissue mass were evident (Fig 3).

Biopsy led to a diagnosis of grade 4 fibroblastic osteosarcoma (Fig 4). As the tumor was thought to be inoperable, radiation therapy was given at a dose of 6300 rads. In September 1971, neuropathy of the left femoral-cutaneous and sciatic nerves occurred, presumably due to neoplastic involvement. By November 1971, the patient had multiple pulmonary metastases, and she died in January 1972.

DISCUSSION

Fibrous dysplasia of the skeleton is an intraosseous neoformation of fibrous tissue probably caused by an anomaly in the development of bone. It was first described by Lichtenstein[3] in 1938 as "polyostotic fibrous dysplasia," and later it became evident that only a single bone or a portion of bone could be involved. In 1942, Lichtenstein and Jaffe[2] described the various possible clinical manifestations of both monostotic and polyostotic fibrous dysplasia, along with extraskeletal abnormalities that could be associated with this disease, such as pigmentation of the skin, premature sexual development, and hyperthyroidism.

Fibrous dysplasia can affect almost any bone, the most common sites being maxilla, proximal femur, tibia, ribs, and pelvis. The distribution and extension of polyostotic fibrous dysplasia vary widely, from the involvement of a few bones to diffuse skeletal involvement. One can distinguish fibrous dysplasias as oligostotic forms, monomelic or hemisomic forms, and generalized forms affecting more than 50% of the body.[4] In the latter two forms, the pelvis is commonly affected. Because fibrous dysplasia

*From the *Department of Orthopedics (Dr Ruggieri is Visiting Clinician), †Department of Diagnostic Radiology, and §Division of Anatomic Pathology, Mayo Clinic and Mayo Foundation, Rochester, MN.*

Reprint requests: Franklin H. Sim, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

Fig 1: Pigmented skin areas with "coast of Maine" borders typical of Albright's syndrome are evident on the left side of the face (A) and on the back (B) of this patient.

Fig 1A.

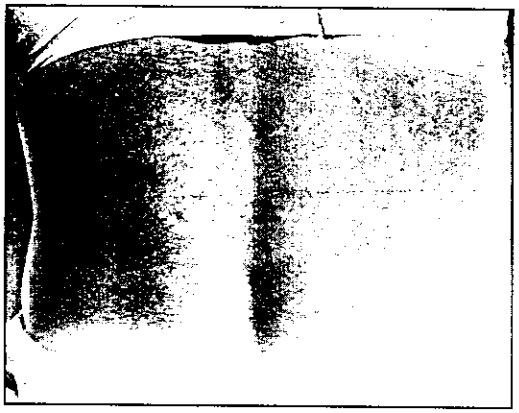

Fig 1B.

has a congenital and hamartomatous origin, it usually manifests in the first 2 decades of life.

Some cases of monostotic or oligostotic fibrous dysplasia are asymptomatic and only become evident incidentally on radiographs in adulthood. The typical radiographic feature is a lytic area with ground-glass appearance (due to the bone formation in the fibrous tissue) (Fig 2), sometimes containing annular radio-opacities or calcifications because of the presence of cartilage. The cortex is often eroded or thinned and is frequently expanded. Bowing of the long bones is often observed. These deformities are due to pathologic fractures. The "shepherd's crook" deformity is a typical feature of fibrous dysplasia affecting the proximal femur. Histologically, there is a proliferation of fibroblasts, producing a dense collagenous matrix with small bone trabeculae. These trabeculae are "embedded" in the fibrous tissue and are not bordered by osteoblasts. The osteoid and osseous trabeculae are generally shaped like "Chinese ideograms." In fibrous dysplasia, the vessels are scarce and thin. At times hemorrhagic and cystic areas can be observed. Cartilaginous tissue also can be present. In adults, fibrous dysplasia usually "matures," showing a reduction of the fibrous proliferative activity and an increase in ossification.

The treatment of fibrous dysplasia is generally conservative, mainly addressed to the correction of deformities and the healing of fractures. In 1937, Albright et al[1] described a syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, and precocious puberty in females. A similar syndrome had already been reported by McCune in 1936.[5] Albright[6] pointed out that the pigmented skin may resemble that seen in neurofibromatosis, but that it differs from it in having irregular and dented borders ("coast of Maine"). Over the years it became evident that the syndrome could include several different forms of endocrine dysfunction, such as acromegaly, hyperthyroidism, hypercortisolism, precocious puberty, and phosphaturic osteomalacia.[7]

Precocious puberty in McCune-Albright syndrome is a form of gonadotropin-independent (gonadotropin-releasing hormone independent) sexual precocity that can affect both females and males.[7] In an attempt to identify a unifying mechanism to explain the autonomous multiple endocrine dysfunction in these patients, some researchers have observed[8,9] that all the involved hormones depend on receptors that are coupled with the G protein-cyclic AMP protein-kinase A-dependent pathway.[7] An activating mutation of the stimulatory G_s protein ($G_s\alpha$) was investigated,[10] and a mutation in $G_s\alpha$, resulting in constitutive activation of adenylate cyclase, was observed in nearly all the affected tissues of patients with Albright's syndrome, including endocrine tissues, skin, and bone.[7,10-12] The finding that this generic mutation is present in a somatic mosaicism explains the various expressions and, therefore, the clinical manifestations of the disease.[7]

The newer molecular biology studies thus confirm what Lichtenstein[13] had actually anticipated, namely that

> fibrous dysplasia has its basis in a genetically complex defect of development in which the clinical picture reflecting the skeletal lesions may be amplified at times by various extraskeletal abnormalities.

That sarcoma may develop in a patient affected by fibrous dysplasia is well known.[14] The first such case was reported by Coley and Stewart in

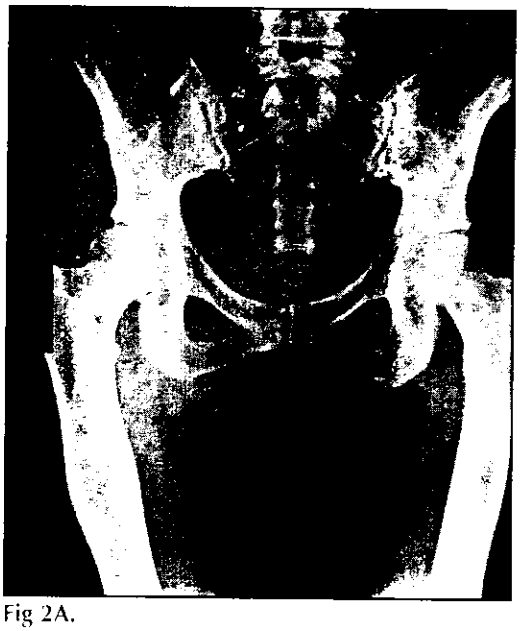

Fig 2A.

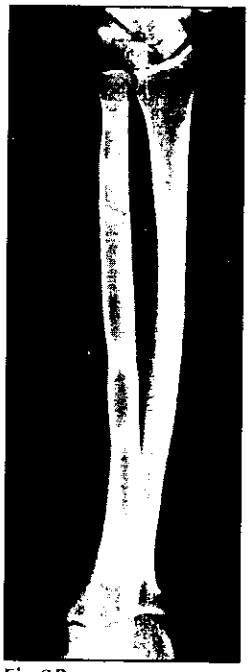

Fig 2B.

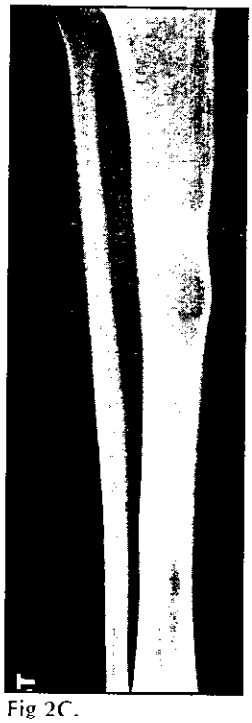

Fig 2C.

Fig 2: Typical radiographic features of fibrous dysplasia (as discussed in the text) are evident in the pelvis and both femurs (A), the right ulna and radius (B), and the right tibia (C).

1945.[15] Subsequently, Schwartz and Alpert[14] in 1964 reported on two cases of their own and 26 cases from the literature.

Sarcomas can occur in both monostotic and polyostotic fibrous dysplasia. Yabut et al, in 1988,[16] in addition to reporting a new case, provided an excellent review of the literature on this subject. In their review of 83 cases, 41 involved monostotic and 31 polyostotic fibrous dysplasia; this type of information was not available for the remaining 11 cases. The histologic features were those of osteosarcoma in 40 cases, fibrosarcoma in 22, and chondrosarcoma in 11. The histology of the remaining 10 cases was not reported.[16]

The incidence of malignant change in fibrous dysplasia has been variably reported as 0.4% to 4%,[16] the highest incidence being found in Albright's syndrome.[14] We believe that for a confident diagnosis of sarcoma in fibrous dysplasia, the histologic evidence of both fibrous dysplasia and sarcoma is required, the only exception being those cases of polyostotic fibrous dysplasia with characteristic clinical and radiographic features of the disease, according to Schwartz and Alpert's criteria.[14] In the present case, the patient had a well-established diagnosis of polyostotic fibrous dysplasia with typical clinical and radiographic features, and she showed all the typical manifestations of Albright's syndrome. The hypertension also could have been due to the endocrine dysfunction. The high level of serum alkaline phosphatase observed in patients with polyostotic fibrous dysplasia may be related to the disease; our patient usually had normal values, which, however, increased when the sarcoma occurred.

In a review of the Mayo Clinic files, 28 cases of sarcoma occurring in fibrous dysplasia were found. Twenty-six of these had histologic evidence of sarcoma and fibrous dysplasia, while 2 had typical polyostotic fibrous dysplasia (1 of the 2 is the present case). There were 19 monostotic and 9 polyostotic forms of fibrous dysplasia. Histologic features were those of osteosarcoma in 19 cases, fibrosarcoma in 5, chondrosarcoma in 3 (1 was a clear cell chondrosarcoma), and malignant fibrous histiocytoma in 1. Most of these sarcomas were high grade. The role of radiotherapy in the occurrence of sarcomas in fibrous dysplasia has been discussed and various opinions have been expressed.[17-19]

Thirteen of the 28 Mayo Clinic patients had prior radiotherapy, and according to the criteria proposed by Huvos et al in 1985,[20] we consider the tumors in these 13 cases as possibly having been radiation-induced. Still, sarcomas in fibrous dysplasia may occur without prior irradiation, as in the present case. In the Mayo Clinic series, 11 of the 19 patients with monostotic fibrous dysplasia in whom sarcoma developed (58%) had received prior irradiation, whereas 7 of the 9 with polyostotic fibrous dysplasia and sarcoma (78%) had not had irradiation. Although these numbers are small, this finding

Fig 3: Osseous destruction of the left ilium proximal to the acetabulum is evident, with a huge and slightly mineralized intrapelvic and extrapelvic soft tissue mass.

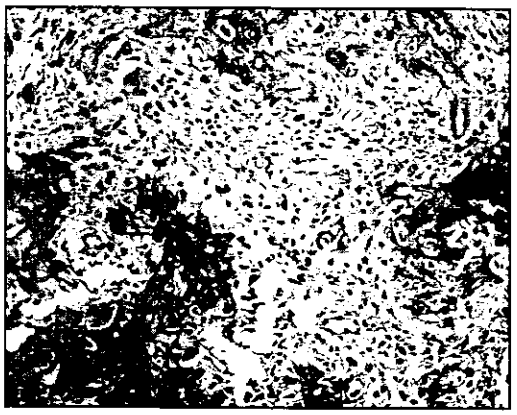

Fig 4A.

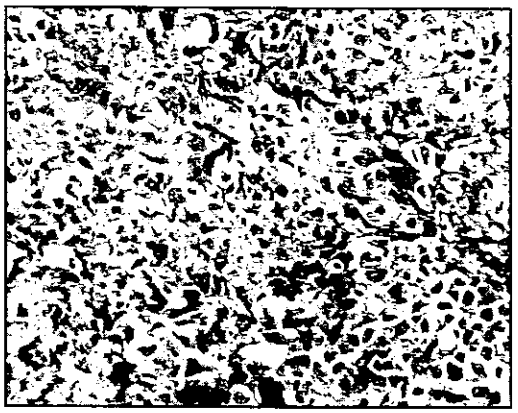

Fig 4B.

Fig 4: High-grade osteosarcoma. Large amount of calcified matrix is present (A, hematoxylin and eosin, ×145). Another area of the sarcoma, showing very atypical-appearing neoplastic cells (B, hematoxylin and eosin, ×145).

seems to indicate that polyostotic fibrous dysplasia has a higher potential for malignant change than does the monostotic form.

Concerning prognosis, of our 9 patients with sarcoma in polyostotic fibrous dysplasia, 5 died of disease, 1 was lost to follow up, and 3 were alive without evidence of disease (the first at 1 year, the second at 5 years, and the third at 7 years). Patients more recently (and therefore more adequately) treated seemed to have a better prognosis. Prognosis is generally poor, however, although it could probably be improved, as with other secondary sarcomas, with early diagnosis and adequate treatment.

To this end, it is important that patients with polyostotic fibrous dysplasia be aware of the possibility of malignant change and report any suspicious new symptoms to their physicians. Any increase in serum alkaline phosphatase levels in a patient with previously normal levels, especially in the absence of pathologic fractures, needs to be investigated. When symptoms occur, radiography, computed tomography, and magnetic resonance imaging are useful in diagnosis.

REFERENCES

1. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases. *N Engl J Med.* 1937; 216:727-746.

2. Lichtenstein L, Jaffe HL. Fibrous dysplasia of bone: a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities. *Arch Pathol Lab Med.* 1942; 33:777-816.

3. Lichtenstein L. Polyostotic fibrous dysplasia. *Arch Surg.* 1938; 36:874-898.

4. Campanacci M. *Bone and Soft Tissue Tumors.* New York, NY: Springer-Verlag; 1990:391-417.

5. McCune DJ. Osteitis fibrosa cystica: the case of a 9-year-old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. *Am J Dis Child.* 1936; 52:743-744.

6. Albright F. Polyostotic fibrous dysplasia: a defense of the entity. *J Clin Endocrinol Metab.* 1947; 7:307-324.

7. Case records of the Massachusetts General Hospital (Case 7-1993). *N Engl J Med.* 1993; 328:496-502.

8. Mauras N, Blizzard RM. The McCune-Albright syndrome. *Acta Endocrinol (Copenh).* 1986; 279(suppl):207-217.

9. Lee PA, Van Dop C, Migeon CJ. McCune-Albright syndrome: long-term follow up. *JAMA.* 1986; 256:2980-2984.

10. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N Engl J Med.* 1991; 325:1688-1695.

11. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the α subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. *Proc Natl Acad Sci USA.* 1992; 89:5152-5156.

12. Shenker A, Sweet D, Spiegel A, Weinstein L. An activating Gs alpha mutation is present in fibrous dysplasia of bone in the McCune-Albright syndrome (abstract). Presented at the 14th Annual Meeting of the American Society for Bone and Mineral Research, Minneapolis, Minn, September 30-October 4, 1992.

13. Lichtenstein L. *Diseases of Bone and Joints.* 2nd ed. St Louis, Mo: CV Mosby; 1975:17-24.

14. Schwartz DT, Alpert M. The malignant transformation of fibrous dysplasia. *Am J Med Sci.* 1964; 247:1-20.

15. Coley BL, Stewart FW. Bone sarcoma in polyostotic fibrous dysplasia. *Ann Surg.* 1945; 121:872-881.

16. Yabut SM, Jr, Kenan S, Sissons HA, Lewis MM. Malignant transformation of fibrous dysplasia: a case report and review of the literature. *Clin Orthop.* 1988; 228:281-289.

17. Tanner HC, Jr, Dahlin DC, Childs DS, Jr. Sarcoma complicating fibrous dysplasia: probable role of radiation therapy. *Oral Surg Oral Med Oral Pathol.* 1961; 14:837-846.

18. Dahlin DC, Unni KK. *Bone Tumors: General Aspects and Data on 8542 Cases.* 4th ed. Springfield, Ill: Charles C. Thomas; 1986:420.

19. Huvos AG, Higinbotham NL, Miller TR. Bone sarcomas arising in fibrous dysplasia. *J Bone Joint Surg.* 1972; 54A:1047-1056.

20. Huvos AG, Woodard HQ, Cahan WG, et al. Postradiation osteogenic sarcoma of bone and soft tissues: a clinicopathologic study of 66 patients. *Cancer.* 1985; 55:1244-1255.